

II. REMARKS

Preliminary Remarks

Claims 1, 2, 4-10, 15, 17-20, 25, 49, 50, and 56 are amended, and claims 3, 16, and 44 are canceled by this response. Claims 1, 2, 4-15, 17-25, 42, 43, and 45-56 are pending following entry of the amendment.

Claims 1, 10, 15, 17, 18, 25, and 56 are amended to more clearly describe the claimed invention; *i.e.*, a method for the treatment or prevention of C-reactive protein (CRP)-mediated tissue damage comprising administering to a subject in need thereof an effective amount of a compound capable of inhibiting the binding of CRP to an autologous or extrinsic ligand thereof, *e.g.*, as described on page 3 (bottom paragraph).

Independent claims 1, 10, and 15 are further amended to specify that the inflammatory and/or tissue damaging condition that is treated or prevented by the claimed method is selected from an infection, an allergic complication of infection, an inflammatory disease, ischemic or other necrosis, traumatic tissue damage and malignant neoplasia, as described on page 6, lines 18-22, and in original claim 3, which is canceled.

References in claims 1, 2, 10, 15, 49, and 50 to an "inflammatory and/or tissue-damaging condition" are deleted in view of the incorporation of the subject matter of claim 3 into claims independent claims 1, 10, and 15 as described above.

Claims 16 and 44, which are directed to a method for treating or preventing atherosclerosis, are canceled.

Claims 4-9, 19, and 20, are amended in their dependencies in accord with the cancellation of claims 3, 16, and 44.

Patentability Remarks

The following declarations by the inventor, Prof. Mark Pepys, are submitted herewith:

- (i) a declaration pursuant to 37 C.F.R. § 1.132 providing experimental data,
- (ii) a Katz declaration pursuant to 37 C.F.R. § 1.132, and
- (iii) a declaration pursuant to 37 C.F.R. § 1.131 swearing behind a reference (Yeh et al.).

Prof. Pepys has reviewed and authorized the filing of the declarations; however, they are being submitted in unexecuted form because Prof. Pepys is currently traveling in foreign countries and cannot execute them at this time. The executed declarations will be submitted shortly under separate cover.

35 U.S.C. §112, first paragraph

Claim 1 is rejected under 35 U.S.C. §112, first paragraph, because the specification is considered to enable one of skill in the art to treat atherosclerosis, but is not considered to provide enablement for preventing atherosclerosis or for treating or preventing tissue damage in general.

The applicant respectfully traverses the rejection of claim 1 under 35 U.S.C. §112, first paragraph, as being enabled only "for treating atherosclerosis." Independent claims 1, 10, and 15 have been amended to be directed to a method for the treatment or prevention of CRP-mediated tissue damage, and are further amended to specify that the tissue damage that is treated or prevented by the claimed invention is associated with a condition selected from the group consisting of an infection, an allergic complication of infection, an inflammatory disease, ischemic or other necrosis, traumatic tissue damage and malignant neoplasia. Original claims 16 and 44, directed to a method for treating or preventing atherosclerosis, are canceled. The applicant submits that the specification fully enables one of skill in the art to practice the claimed method for treating or preventing CRP-mediated tissue damage successfully without having to perform undue experimentation, as discussed below. Furthermore, the applicant disagrees with the examiner's allegation that the application is enabled for a method for treating or preventing atherosclerosis *per se*.

Background

Atherosclerosis is a disease wherein the arterial inner wall thickens. If it becomes sufficiently severe it can reduce arterial blood supply to the heart, brain or periphery causing vascular insufficiency. An atherothrombotic event can occur as a complication of atherosclerosis in which an atherosclerotic plaque ruptures, triggering thrombotic occlusion of the effected artery and ischemic necrosis of the tissue supplied by that artery (*i.e.*, infarction - tissue damage resulting from obstruction of the blood supply). The tissue damage (ischemic necrosis) resulting from or associated with atherosclerosis is the cause of

death in about half of all individuals. The current best informed opinion is that CRP does not play a significant role in the pathogenesis of atherosclerosis. The observations set out in the present application and related academic papers by the Pepys group do not address prevention or treatment of either atherosclerosis or atherothrombosis. Again, please note that the original claims 16 and 44, which refer to treating or preventing atherosclerosis, are canceled.

Enablement

The amended claims of the present application are clearly directed to a method for the treatment or prevention of CRP-mediated tissue damage. As described in the application, and as specified in amended claims 1, 10, and 15, the tissue damage that is treated or prevented by the claimed invention is associated with a condition selected from the group consisting of an infection, an allergic complication of infection, an inflammatory disease, ischemic or other necrosis, traumatic tissue damage and malignant neoplasia. As further specified in claims 2, 4-9, 17, 18, 49, 50, and 56, tissue damage that can be treated or prevented by the claimed invention includes tissue damage associated with any of the following conditions: atherosclerosis or a complication of atherosclerosis; a bacterial, viral, or parasitic infection; an allergic complication of rheumatic fever, glomerulonephritis, or erythema nodosum leprosum; an inflammatory disease selected from rheumatoid arthritis, juvenile chronic (rheumatoid) arthritis, ankylosing spondylitis, psoriatic arthritis, systemic vasculitis, polymyalgia rheumatica, Reiter's disease, Crohn's disease and familial mediterranean fever; tissue necrosis selected from myocardial infarction, tumor embolization and acute pancreatitis; trauma selected from elective surgery, burns, chemical injury, fractures and compression injury; malignant neoplasia selected from lymphoma, Hodgkin's disease, carcinoma and sarcoma; and stroke, whether it is a complication of atherosclerosis or has other causes. It must be kept in mind that the claimed method is for the treatment or prevention of CRP-mediated tissue damage that is associated with said condition.

The present application describes results obtained using an experimental *in vivo* model system in which tissue damage is caused by obstruction of blood supply and provides the first, and up to the present time the only, direct *in vivo* demonstration that CRP exacerbates tissue damage. The present application provides the first experimental evidence that CRP contributes to tissue damage *in vivo*, and that removal of CRP function from a

subject who has an inflammatory and/or tissue damaging condition involving elevated levels of CRP will treat or prevent tissue damage in that subject. Accordingly, the claims of the present application are directed to a method for treating or preventing such CRP-mediated tissue damage. The beneficial effects of the claimed invention are obtained for any inflammatory and/or tissue damaging condition involving elevated levels of CRP. The invention is therefore generally applicable. The application demonstrates that CRP contributes to tissue damage in general, as exemplified with reference to myocardial infarction in a rat model. Rats were treated to promote myocardial infarction. Infarct size was measured in the presence and absence of human CRP. Infarct size gives a direct measurement of the amount of tissue damage in the subject. The results are indicated in the section bridging pages 29 and 30 of the present application, and in Table 2. Table 2 provides data that shows that in animals receiving human CRP the mean infarct size is increased to be about 40% larger than in control animals that do not receive CRP. These results therefore demonstrate that the extent of tissue damage *in vivo* is directly affected by and increased in the presence of human CRP; *i.e.*, that human CRP directly exacerbates tissue damage *in vivo*.

Using a different experimental *in vivo* model system from that described in the present application, the inventor, Professor Mark Pepys, has demonstrated that human CRP contributes to tissue damage in the brain in the manner previously demonstrated for the heart. Gill et al. (*J. Cerebral Blood Flow & Metabolism*, 24(11):1214-1218, 2004), which is co-authored by Prof. Pepys, describes experimental results that show that damage to brain tissue (infarct size) resulting from obstruction of blood supply is significantly greater in rats receiving human CRP than in control rats that do not receive CRP. See page 3, second paragraph of Gill et al., a copy of which was submitted with the response filed on November 29, 2004. Gill et al. therefore presents further compelling *in vivo* evidence that CRP contributes to tissue damage in general.

The present application provides evidence concerning the conditions that are associated with tissue damage that involves elevated levels of CRP, thereby permitting one of skill in the art to identify type of tissue damage that can be prevented or treated in accordance with the present invention. As described in the present application "CRP is the classical acute phase protein, the circulating concentration of which increases dramatically in response to most forms of inflammation, tissue injury and infection, and the value (*i.e.*, the amount of

CRP) attained in most conditions correlates closely with the extent and activity of disease.” See page 1, lines 11-15, citing an article by the present inventor in the Oxford Textbook of Medicine (3rd Ed., Vol. 2, 1996; identified as reference FR in the IDS filed July 9, 2001). This article teaches that a number of inflammatory and/or tissue damaging conditions are associated with increased CRP production and major elevation of serum CRP concentration, including infections, allergic complications of infections, inflammatory disease, allograft rejection, malignant neoplasia, necrosis and trauma (see page 1528 and Table 2 on page 1529). The present application similarly teaches that inflammatory and/or tissue damaging conditions associated with elevated CRP levels for which tissue damage may be prevented or treated according to the claimed invention include infections, allergic complications of infection, inflammatory diseases, ischemic or other necrosis, traumatic tissue damage and malignant neoplasia (see page 6, lines 18-22). The application identifies tissue-damaging conditions associated with elevated CRP levels and describes therapeutic agents that can be administered to inhibit CRP and prevent or treat exacerbation of tissue damage by CRP. Once in possession of the compelling and direct *in vivo* evidence provided in the present application, a person of skill in this art would have information sufficient to practice the invention as claimed. The application clearly describes and provides guidance, direction, and working examples for treating and/or preventing the tissue damage associated with the specified inflammatory and/or tissue damaging conditions according to the claimed invention.

In vivo data support

The ability of one of skill in the art to successfully practice the claimed invention as described by the present application is further demonstrated by the additional experimental data obtained by the applicant that is described in a declaration pursuant to 37 C.F.R. § 1.132 by Prof. Mark Pepys that is submitted herewith. The data demonstrate again the specific exacerbation of tissue damage mediated by human CRP in the rat acute myocardial infarction model, and clearly show that *in vivo* administration of a specific inhibitor of CRP completely abrogates this pathogenic effect. See the data in Table I and the description of the results on pages 5-6 of the declaration. The experimental results described in the declaration further demonstrate that the extent of tissue damage that occurs *in vivo* is directly related to and exacerbated by the presence of CRP in a subject. The inhibitor of CRP

that was used to obtain the additional experimental results is the phosphocholine derivative 1,6-bis(phosphocholine)-hexane, which consists of a pair of phosphocholine molecules that are connected by a short (6-carbon) alkane linker (*see* Formula I on page 13 of the present application).

The data described in the inventor's declaration has been submitted in a manuscript to *Nature*, arguably the leading peer-reviewed scientific journal in the world. The manuscript has been favorably reviewed, accepted for publication, and will shortly be published.

Specific points raised by Examiner

As discussed below, in stating the grounds for the rejection under 35 U.S.C. §112, first paragraph, the examiner has incorrectly characterized the claimed invention, most likely through a misunderstanding of the presently claimed invention. Referring to the preamble to claim 1, the examiner acknowledges that the claims are directed to treating and/or preventing tissue damage in a subject having an inflammatory and/or tissue damaging condition; however, the examiner objects to the claim under 35 U.S.C. §112, first paragraph, because the term "tissue damaging condition" is considered to include all disorders. The examiner further argues that, "the underline (sic) etiology of atherosclerosis, as well as other diseases associated with tissue damaging (cancers, Alzheimer, etc.) are complex and unclear," and alleges that "the instant claims read on preventing and/treating preventing and/treating (sic) all diseases associated with tissue damage, necessitating an exhaustive search for embodiments suitable to practice the claimed invention, absent undue experimentation." *See* page 3, line 15, to page 4, line 2.

In setting forth arguments in support of the rejection under 35 U.S.C. §112, first paragraph, the examiner incorrectly suggests that the purpose of the claimed invention is to prevent or treat tissue-damaging disorders such as atherosclerosis, cancer, Alzheimer's disease, and viral infection, rather than the tissue damage caused by such disorders, which is the adverse response that is actually treated or prevented by the claimed invention. For example, the examiner refers to disorders such as atherosclerosis, cancer, Alzheimer's disease, and viral infection, and argues that, "[t]he state of the art in treating such diseases is low;" that "[t]here is no established method for preventing such disease in the art," and that "the specification provides no further guidance, direction, or working examples as how the claimed method would be effective in preventing atherosclerosis." *See* page 3, lines 8-14.

The examiner is correct in observing that the applicant has provided evidence showing that the disclosed CRP inhibitors suppress the pathogenic effect of CRP. The experimental results described in the above-discussed inventor's declaration under 37 C.F.R. § 1.132 directly demonstrate this. On the other hand, the examiner statement that "[i]t is known that excess amounts of human CRP would induce myocardial infarction," for which the applicant's own work (Griselli et al.) is cited (*see* page 3, lines 9-11), is incorrect. The application does not describe, and neither Griselli et al. nor any other work published to date provides evidence or suggests that CRP induces myocardial infarction under any circumstances. Moreover, the examiner's arguments in support of the rejection under 35 U.S.C. §112, first paragraph, are misdirected, because the claimed invention is not directed to treating and/or preventing the underlying inflammatory and/or tissue damaging conditions that cause the tissue damage, as alleged by the examiner. The application is concerned with the treatment or prevention of tissue damage caused by high circulating concentration of CRP in subjects having certain underlying primary conditions. Experimental evidence in the present application and published by the applicant confirms that CRP contributes to tissue damage in general, and the present application further demonstrates that subjects having a certain range of conditions would be encompassed by the present application because those conditions involve elevated CRP levels. The application makes it explicitly clear that any individual with pre-existing tissue damage and simultaneously having increased CRP concentration is at risk of suffering exacerbation of the tissue damage and thus is a suitable candidate for beneficial treatment with a drug that inhibits CRP.

The applicant strongly disagrees with the examiner's allegation that the term "tissue damaging condition" as used in the application includes all disorders. As discussed above, claim 1 has been amended to identify a selected set of conditions associated with tissue damage accompanied by an elevated level of CRP, for which the claimed method will operate successfully to treat or prevent CRP-mediated tissue damage. In particular, claim 1 clearly specifies that the tissue damage that is treated or prevented by the claimed method is associated with a condition selected from the group consisting of an infection, an allergic complication of infection, an inflammatory disease, ischemic or other necrosis, traumatic tissue damage and malignant neoplasia. The specification provides a sound and compelling scientific basis for the breadth of the present claims. All of the information needed by a person of skill in the art may be found in the application, and undue experimentation would

not be required to practice the claimed method successfully. The application therefore enables one of skill in the art at the time of filing to practice the claimed invention successfully without having to perform undue experimentation.

In view of the foregoing, withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejections in view of prior art

In regard to all of the rejections of claims in view of the prior art, the applicant wishes to emphasize that the present claims are directed to a method for the treatment or prevention of CRP-mediated tissue damage in a subject. As discussed above with respect to enablement issues, such CRP-mediated tissue damage may occur in association with a variety of inflammatory or tissue-damaging conditions, including atherosclerosis. However, original claims 16 and 44, directed to a method for treating atherosclerosis, are canceled by this response (to expedite prosecution and without prejudice to the applicant's right to submit similar claims in a continuing application), and the present claims are not directed to a method for treating atherosclerosis per se, as the examiner alleges is described by the references cited as prior art.

35 U.S.C. §103(a)

(1) Claims 1-25 and 42-56 are rejected under 35 U.S.C. §103(a) as being obvious in view of Bhakdi et al. and Kitao, further in view of Yedgar et al. (U.S. Patent No. 5,064,817) and Wissner et al. (U.S. Patent No. 4,640,913).

The applicants respectfully traverse this rejection. All four of the references cited as prior art are described by the examiner as teaching that phosphorylcholine and its derivatives are useful for treating atherosclerosis or hypertension, "an underlying etiology of atherosclerosis" (see paragraphs 4 and 6 of the official action).

Bhakdi et al.

In paragraph 4 of the official action, the examiner asserts that Bhakdi et al. and Kitao teach that phosphorylcholine is useful for inhibiting the binding of CRP to LDL, "wherein the

binding of CRP to LDL is known to be a factor of atherosclerosis." The significance of this statement is unclear. What is meant by "factor of atherosclerosis?" Is the examiner suggesting that CRP is a pathogenic factor in atherosclerosis? The examiner appears to allege that the teachings of Bhakdi et al. and Kitao would have provided a suggestion or motivation to one of ordinary skill in the art at the time the invention was made to treat atherosclerosis by administering an agent that inhibits the binding of CRP to its ligand. This allegation is incorrect. Phosphocholine has been known to be the highest affinity small molecule ligand for CRP since 1971, and it is known to be inhibitory for all known calcium dependent ligand binding interactions of CRP. The binding of CRP to LDL, first discovered and characterized by the applicant, Professor Pepys in 1984 and cited in the present application (ref. no. 5), led Prof. Pepys to make the first suggestion that CRP might be involved in atherosclerosis. Many subsequent publications have included similar speculations but up to the present time there have been no observations that demonstrate any actual role of CRP in atherosclerosis, atherogenesis or atherothrombosis *in vivo*. Indeed, as stated above, the overwhelming weight of current published evidence, both from clinical studies and animal models, indicates that CRP has neither an atherogenic nor an atheroprotective role *in vivo*.

Bhakdi et al. demonstrates *in vitro* binding of CRP to E-LDL, and shows *ex vivo* that CRP is co-localized with E-LDL in coronary artery specimens. Based on the demonstration that CRP enhances the *in vitro* conversion of complement factor C3 by E-LDL, Bhakdi et al. speculates that CRP may promote pathological events in atherogenesis via complement activation. However, Bhakdi et al. presented no evidence that CRP promotes or causes atherogenesis in any way, or has any pathological effect on tissue lesions. In fact, as noted above, while there has been considerable speculation over the years, there is no *in vivo* evidence at all that CRP causes atherosclerosis or atherothrombosis.

At the time the invention was made, persons of ordinary skill in the art would have recognized that the mere presence of CRP and LDL together at the same tissue site, with or without complement activation, does not prove or even suggest that CRP is pathogenic, pro-atherogenic or pro-atherothrombotic. One of ordinary skill in the art would have recognized that protein binding and complement activation are as likely to lead to beneficial opsonization and phagocytic clearance of harmful LDL and E-LDL as to cause exacerbation of damage by these lipoproteins. By analogy, the presence of an individual at the scene of a

crime does not mean that this individual is the perpetrator of the crime; he could be the criminal or an accessory, but equally well could be an innocent bystander, a rescuer, a policeman, fireman, etc. Moreover, as the applicant has pointed out in previous responses, a number of scientific articles which are representative of the general knowledge at the time the invention was made suggested that CRP is atheroprotective. For example, Steel et al. (*Immunology Today*, 1994, 15:81-89), and Kilpatrick et al. (*Immunology Research*, 1991, 10:43-53), submitted with the response filed on May 14, 2004, both consider CRP to have beneficial activities, including opsonization, incomplete complement activation, enhancement of phagocytosis in neutrophils and macrophages, enhancement of natural-killer activity and modulation of platelet activation. These are set out in Figure 2 of the review by Steel et al. on page 84. Steel et al. further teach that acute phase proteins such as CRP "can directly neutralize inflammatory agents, help to minimize the extent of local tissue damage, as well as participate in tissue repair and regeneration" (*see* page 82). An important point emerges from the review by Kilpatrick et al. concerning complement activation by CRP complexes. The authors note that CRP-initiated activation of the classical pathway of complement leads to the assembly of an effective C3-convertase, which is attributed to a host defense-related function. The reference teaches that CRP complexes do not appear able to lead to the formation of an efficient C5-convertase, and that "CRP-initiated complement activation may not generate the complement chemotactic factor C5a and the cell membrane lytic complex C5b-9" (*see* the passage bridging pages 47 and 48). Other references published at the time the invention was made confirmed that CRP-dependent activation of complement is incomplete, resulting in conversion of factor C3, with minimum activation of the components of the membrane attack complex (C5 through C9). For example, *see* Mold et al. (*Immunopharmacology*, 1999, 42:23-30), and Berman et al. (*J. Immunology*, 1986, 136(4):1354-1359), copies of which are submitted herewith. Both of these references teach that CRP is involved in the early classical complement activation pathway leading to production of non-lytic components such as C3, without activation of the tissue-damaging membrane attack complex (*see* Berman et al., page 1358; Mold et al., page 25). Moreover, in view of the incomplete activation of complement by CRP, Mold et al. proposes that CRP may help limit the inflammatory response by providing opsonisation with minimum generation of C5a and C5b-9 (*see* page 29).

As discussed above, Bhakdi et al. based their suggestion that CRP may promote atherogenesis via complement activation on the observation that CRP enhances the *in vitro* conversion of complement factor C3 by E-LDL. However, this result would not be regarded by one of ordinary skill in the art as evidence that CRP is pathogenic, since it was well known by persons of ordinary skill in the art that CRP-initiated complement activation is incomplete and fails to result in production of C5a and C5b-9, and formation of the tissue-damaging membrane attack complex, as discussed above. Therefore, the conclusion drawn by Bhakdi et al. that CRP may promote pathological events by complement activation would have been treated with deep suspicion by those skilled in the art at the time of the present invention.

In their later 2004 paper that retracted their suggestion that CRP promotes atherosclerosis, Bhakdi et al. acknowledged that the assay used in their 1999 paper would only have detected activation of the early complement pathway by CRP, and referred to the results described in the above-discussed articles by Mold et al. and Berman et al. as a reason for questioning their earlier conclusion that CRP contributes to the immunopathogenesis of atherosclerosis (Circulation, 109:1870-1876; see page 1871, top left column, referring to references 17 and 18). The Bhakdi et al. 2004 reference concludes that CRP-mediated complement activation promotes the removal of debris from tissues, thereby preventing an inflammatory reaction, and that the activation of complement that is associated with tissue damage is caused by high levels of E-LDL and is CRP-independent (see page 1874, right column). The examiner's allegation that the Bhakdi et al. 2004 article can be interpreted to "clearly indicate the usefulness of inhibiting CRP activities for reducing the development of atherosclerosis" (see page 9 of the official action) is thus unsupported by the reference and is incorrect.

To establish a *prima facie* case of obviousness, the examiner must show that the prior art references themselves or the knowledge generally available to one of ordinary skill in the art would (1) provide some suggestion or motivation to modify or combine reference teachings to obtain the claimed invention, (2) teach or suggest all of the claim limitations, and (3) provide a reasonable expectation that the claimed invention can be made or used successfully. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See M.P.E.P. § 2142.

In determining if there is obviousness in the first instance, "it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Finc*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See M.P.E.P. § 2142.

The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Obviousness does not require absolute predictability, however, at least some degree of predictability is required. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure." *In re Vaack*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Combining prior art references without evidence of a suggestion, teaching, or motivation "simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight." See *Ecolchem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 1371-72; 56 U.S.P.Q.2d 1065 (C.A.Fed. - Cal., 2000).

The applicants submit that the combination of Bhakdi et al. and Kitao, Yedgar et al. (U.S. Patent No. 5,064,817) and Wissner et al. (U.S. Patent No. 4,640,913) would not have provided suggestion, teaching, or motivation to practice the claimed invention with a reasonable expectation of success, and that the rejection of the claims under 35 U.S.C. § 103(a) as allegedly being obvious in view of Bhakdi et al., in combination with the secondary references, can only be based on hindsight in view of the teachings of the present application, and is improper.

As discussed above, the claims are directed to a method for the treatment or prevention of CRP-mediated tissue damage in a subject comprising administering to a subject in need thereof an effective amount of phosphocholine or a derivative thereof that

binds to CRP and inhibit its binding to an autologous or extrinsic ligand, whereas the prior art relates to speculative possible treatments of atherosclerosis. Not only is the teaching of the prior art distinct from the claimed method, but one of ordinary skill in the art would not have reasonably expected the teaching of the prior art to operate successfully. As discussed above, Bhakdi et al. (1999) provided no evidence that inhibition of CRP activity is expected to confer therapeutic benefit. One of ordinary skill in the art would have known that other prior art references available at the time the invention was made clearly suggested that CRP has a beneficial, protective role, due to its incomplete activation of complement, and would have recognized that the assay of activation of C3 used by Bhakdi et al. detects the activation of the early complement pathway, but not of the later tissue-damaging complement pathway. Therefore, one of ordinary skill in the art at the time the invention was made would reasonably have doubted whether administration of a CRP inhibitor to a subject would successfully prevent or treat atherosclerosis.

The secondary references cited by the examiner would not have overcome this skepticism of one of ordinary skill in the art towards the teachings of Bhakdi et al. (1999).

Kitao

The Kitao abstract teaches that the *in vitro* binding of CRP to serum lipoproteins is inhibited by phosphorylcholine and 6-amino-n-caproic acid, and indicates that "the relationship of CRP and atherosclerosis is discussed." Kitao neither discloses or suggests that CRP plays any role in the pathogenesis of atherosclerosis or atherothrombosis. Given that CRP was not known to have a role in the pathogenesis of atherosclerosis at the time that Kitao was published, Kitao at most can be considered to provide a suggestion to use an inhibitor of the binding of CRP to serum lipoproteins such as phosphorylcholine and 6-amino-n-caproic acid in a program of basic research in order to discover whether or not CRP has any active role, protective or pathogenic, in relation to atherosclerosis.

Yedgar et al. and Wissner et al.

Yedgar et al. describes ethylene glycol and glycerol derivatives that inhibit PLA₂, and suggests that such compounds can be administered to treat pathological conditions associated with oversecretion of PLA₂, including atherosclerosis. Phosphocholine is just one of a long list of possible derivatives which is suggested. Phosphocholine derivatives are not tested *in vivo* and phosphatidylethanolamine and phosphatidylserine derivatives are preferred.

Wissner et al. describes phosphocholine derivatives which are suggested to have anti-hypertensive action. However, the applicant believes that no drugs containing or derived from phosphocholine are in use as anti-hypertensives. The relevance of the Yedgar et al. and Wissner et al. references to the issue of the alleged obviousness of the claimed invention is unclear. The examiner states that "Yedgar et al. teaches that various phosphorylcholine derivatives are known to be useful for treating pathological conditions such as atherosclerosis," and that "Wissner et al. teaches various phosphorylcholine derivatives are useful for treating hypertension, an underlying etiology of atherosclerosis," (see page 5 of the official action). However, nothing in Yedgar et al. or Wissner et al., or in either of the other references cited by the examiner, suggests that the compounds disclosed by Yedgar et al. or Wissner et al. are capable of binding to CRP and inhibiting its activity. One of ordinary skill in the art would not reasonably assume that phosphocholine derivatives described by Yedgar et al. as being capable of inhibiting PLA₂, or those described by Wissner et al. as being anti-hypertensive, would also bind to CRP and prevent it from binding to its ligands. Furthermore, even if any of the disclosed phosphocholine derivatives were shown to inhibit the binding of CRP to its ligands, one of ordinary skill in the art would not have reasonably expected the inhibition of CRP to confer therapeutic benefit for the reasons discussed above. Therefore, one of ordinary skill in the art would not reasonably have considered combining the teachings of Yedgar et al. and Wissner et al. with those of Bhakdi et al., alone or in combination with Kitao, to obtain the claimed invention.

For the reasons discussed above, the applicant submits that the claimed invention would not have been obvious to one of ordinary skill in the art at the time the invention was made, and respectfully requests that the rejection of claims 1-25 and 42-56 under 35 U.S.C. §103(a) in view of Bhakdi et al., Kitao et al., Yedgar et al., and Wissner et al. be withdrawn.

(2) Claims 1-25 and 42-56 are rejected under 35 U.S.C. §103(a) as being obvious in view of Bhakdi et al. and Griselli et al., further in view of Yedgar et al. (U.S. Patent No. 5,064,817) and Wissner et al. (U.S. Patent No. 4,640,913).

The teachings of Bhakdi et al., Yedgar et al., and Wissner et al., as they relate to the claimed invention are discussed above.

Griselli et al.

Professor Mark Pepys, the inventor of the claimed invention, is a co-author of the Griselli et al. paper on which the present patent application is based. Submitted herewith is a Katz declaration pursuant to 37 C.F.R. § 1.132 by Prof. Mark Pepys which declares that he is the sole inventor of the subject matter disclosed in the present application, and that the individuals listed as co-authors of the Griselli et al. paper worked under his supervision, and were not co-inventors. Accordingly, Griselli et al. is not considered to be available as prior art.

Without Griselli et al., the claims stand rejected in view of Bhakdi et al., in combination with Yedgar et al., and Wissner et al. The claimed invention would not have been obvious to one of ordinary skill in the art at the time the invention was made in view of these references, for the reasons discussed above. Therefore, the applicant respectfully requests that the rejection of claims 1-25 and 42-56 are rejected under 35 U.S.C. §103(a) in view of Bhakdi et al., Griselli et al., Yedgar et al., and Wissner et al., be withdrawn.

(3) Claims 1-25 and 42-56 are rejected under 35 U.S.C. §103(a) as being obvious in view of Yeh et al. (U.S. Patent No. 6,764,826) in view of Bhakdi et al., further in view of Yedgar et al. (U.S. Patent No. 5,064,817) and Wissner et al. (U.S. Patent No. 4,640,913).

Yeh et al.

The effective date of U.S. Patent No. 6,764,826 of Yeh et al., cited as the primary reference, is June 8, 2000, which is the date that the patent is effective as a 102(e) reference (see 37 C.F.R. §1.131(a)(1)). The effective date of U.S. Patent No. 6,764,826 of Yeh et al. is therefore later than a year prior to the filing date of the present application, which was filed